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Case Report

Type 1 Von Willebrands disease presenting as menorrhagia in adolescent girl

Rajani H S[1,*], **Akshaya SV**[1]

[1] *Dept. of Pediatrics, JSS Medical College, JSS Academy of Higher Education and Research, Mysore, Karnataka, India*

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ABSTRACT

Type 1 Von Willebrand disease (VWD) is the most common type of VWD due to partial quantitative deficiency of Von Willebrand factor (VWF) which is essential for hemostasis. It is inherited in an autosomal dominant pattern in most cases, but variable penetrance has also been observed in certain cases. In the present report, we report a case of 11-year-old admitted a tertiary hospital with complaints of excessive vaginal bleeding (menorrhagia), and fatigue since the past 12 days. At the age of 10 years, there was excessive bleeding from the injured site in the knee following a fall on the ground. Blood investigations revealed anemia, a decrease in Von Willebrand antigen, and collagen binding assay. USG reports showed polycystic morphology of the left ovary with thickened endometrium. There is no complete cure for this condition. Mild bleeding episodes during the menstrual cycle can be managed using oral contraceptive pills. Desmopressin has been proven to be useful in mild cases especially to achieve normal levels before medical procedures or surgery but not in severe forms of Type 1 VWD. In severe forms of Type 1 VWD, VWF concentrates have been tried.

1. Introduction

Von Willebrand disease is the most common inherited bleeding disorder with an estimated prevalence of approximately 10% in India.[1] VWD remains an undiagnosed entity in India. Dr.Erik von Willebrand from Finland was the first to describe this condition in 1926. Von Willebrand factor, a large multimeric glycoprotein synthesized in megakaryocytes and endothelial cells have two important roles-aids in platelet plug formation and thus binding it to the site of endothelial injury; binds and transports factor VIII thus preventing factor VIII degradation.[2] VWF deficiency leads to bleeding from mucocutaneous sites. Three types of VWD have been described. Type 1 and 3 VWD are due to partial quantitative deficiency of VWF and complete quantitative deficiency of VWF respectively whereas type 2 VWD is due to severe qualitative defects in VWF. Type 1 VWD is usually mild and remains undiagnosed. Affected individuals usually present with mild bleeding from mucocutaneous areas. Rarely, affected individuals develop severe symptoms. In a study done by Koudies et al, menorrhagia resulted in blood cell transfusions in 6% of type 1 VWD patients.[3] Hereby, we report a case of an 11-year-old female child who presented with menorrhagia and severe anemia which required blood transfusion and was later diagnosed to have Type 1 Von Willebrand disease.

2. Case Report

An 11-year-old developmentally normal female child was admitted to the PICU with complaints of excessive vaginal bleeding for 12 days. It was not associated with clots, 5-6 pads/day. No history of dysmenorrhea. No h/o gum bleed,

* *Corresponding author*.
E-mail address: rajanihs@jssuni.edu.in (Rajani H S).

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petechiae, epistaxis, mucosal bleed. No h/o haematemesis, melena. No history of painful swollen joints. No history of fever with bleeding episodes. No history of breathlessness, or fatigue on daily activity. No h/o recent weight gain, weight loss, cold, or heat intolerance. History of excessive bleeding after injury to the knee in January 2019 (details not available). No significant/relevant family history is present. She attained menarche at the age of 9 and half years and from that age every month she had regular cycles for 6 months followed by 2 months of amenorrhea. Following this, the child had menorrhagia for 7 days associated with clots, and changed 4-5 pads/day. The child was shown in a local hospital and was started on Tab. Norethisterone for 1 month. Ultrasound abdomen showed a left simple ovarian cyst. The child had regular cycles for the next 3 months followed by amenorrhea for the next 3 months. This month, when the child had cycles she had menorrhagia for 12 days. On the day of admission, the child did not have menstrual bleeding. The child was conscious, and lethargic on admission. On General examination, vitals were stable except for tachycardia. Severe pallor with hyperpigmentation of knuckles was seen. Systemic examination was unremarkable. A complete hemogram revealed that abnormal hemoglobin (4.6 g/dl) with normal platelet count and total count of Iron, Ferritin was low. TIBC was elevated. Folic acid was normal. Vitamin B12 was low. PT and APTT were mildly elevated. Bleeding time and clotting time was normal. The thyroid profile was found to be within normal limits. USG Abdomen and Pelvis revealed a normal right ovary with a mildly bulky left ovary with few enlarged follicles measuring 12-20mm, thickened endometrium of 11.5mm which is more than the normal limits. The child was transfused with 2 pints of PRBC in a gap of 24 hours. A gynaecologist opinion was sought and was asked to start on Tab. Norethisterone. Repeat investigations on day 3 revealed improvement in Haemoglobin levels (9.5g/dl) with normal platelet counts. Given significant past history, child was planned to workup for von Willebrand disease. The child was discharged after becoming clinically and hemodynamically stable.

The child was followed up with a Paediatric hematologist. Von Willebrand's workup was done 12 days post-discharge. A complete hemogram revealed Hb-9.3g/dl with normal platelet counts. Prothrombin time, APTT, Fibrinogen level, and Thrombin time were normal. Factor VIII and Factor IX assays were mildly deranged. VWF Antigen and collagen binding assay were low. Platelet aggregation studies (ADP, Arachidonic acid, collagen, ristocetin) were within normal limits. Hence a diagnosis of Type 1 Von Willebrand Disease was made.

3. Discussion

Von Willebrand Disease type 1 is the most common (60-80%) among VWD.[4] It is due to partial quantitative deficiency of the Von Willebrand factor. Usually, most of the patients are asymptomatic. Some present with mild to moderate bleeding and is incidentally detected.[5] Von Willebrand factor, a large multimeric glycoprotein synthesized from megakaryocytes and endothelial cells are essential for attaining hemostasis. Von Willebrand disease type 1 is inherited in an autosomal dominant pattern with an estimated prevalence of 18% according to a study done by Trasi et al in India.[1] Finnish physician Erik von Willebrand described this condition initially and menorrhagia was the common presentation that he noted. The frequency of menorrhagia in patients with Von Willebrand disease varies between 5-20% in various studies.[6–11]

The symptoms and severity of this condition can vary between individuals. Some individuals may be asymptomatic and diagnosed as a result of significant family history or blood workup prior to any procedure. Certain individuals might be identified during procedures like tonsillectomy where they bleed profusely. Some individuals may present with menorrhagia but are often left undiagnosed. In type 1, mild symptoms most likely occur, like mucocutaneous bleeding (Eg: Epistaxis, gum bleeding, menorrhagia). Severe menorrhagia leading to anemia or requiring blood transfusion was reported in 6%, dilatation and curettage in 17%, and hysterectomy in 13% according to a study done in New York.[3] The diagnosis of this condition can be made with the identification of symptoms. Detailed family history will be helpful in most cases as it is an autosomal dominant inherited condition. The VWF Antigen and VWF Ristocetin co-factor activity is usually decreased. Factor VIII levels remain normal. The Complete blood count to check the hemoglobin levels (to see the severity of anemia) and Platelet counts are noted as they are usually normal in VWD type 1. Usually, the prothrombin time is normal in a patients with VWD. Genetic testing might help confirm the diagnosis.

There is no cure for Von Willebrand type 1. In the case of menorrhagia, Oral contraceptives are given. It is found to reduce menstrual blood flow in certain studies whereas poor response was noted in one study.[12] Desmopressin is found to increase plasma vWF and factor VIII levels. It is not useful in severe cases of VWD or a rare type called Type 1C vWD Antifibrinolytic agent such as tranexamic acid also helps in reducing menstrual loss.[12] VWF concentrates have been found to be useful in severe type 1 VWD. Counseling the patient and the parents regarding the condition, its prognosis, treatment and especially prevention injuries should be explained and forms the main part of the care plan.

4. Conclusion

This case helps us in understanding the clinical presentation and diagnosis of the patient with type 1 VWD. Although type 1 VWD is a very common condition, it goes unnoticed because abnormal uterine bleeding is common and often

Table 1: Blood investigations

Investigations	14/12/2020	15/12/2020	16/12/2020	29/12/2020
Hemoglobin (N = 11.5–15.5 g/dl)	4.6		9.5	9.3
Hematocrit (N = 35%–45%)	14.9		30.9	29.2
WBC (N = 4,000–11,000 cells/mm^3)	14,860		9090	8800
Platelets (N = 1.5–4,5 lakh cells/mm^3)	2,80,000		2,25,000	2,27,000
Reticulocyte count (N=2-5%)	7.55			
MCV (N=77-95 fl)	67.9		79.2	73
MCH(N=25-33pg)	20.7		24.4	23.1
MCHC(N=33.5-35.5g/dl)	30.5		30.7	31.9
RDW (N=12-14.5%)	19.3		20.5	
PT (CONTROL=13.1 seconds)	14.2			13
INR (N = 1.1 or below)	1.1			
aPTT (Control=28.7 seconds)	33.8			28
Bleeding time(N=2-5min)		3		
Clotting time (N=3-8 min)		5		
Fibrinogen level (N=200-400 mg/dl)				331
Thrombin time (N=18-22 seconds)				19.5
Factor VIII Assay (N=50-150%)				180
Factor IX Assay (N=50-150%)				160
VWF-RICOF Assay (N=50-200%)				50
VWF-Antigen (N=60-150%)				40
VWF-Collagen binding assay (N=40-250%)				34.5
ADP (Normal=50-100%)				76
Arachidonic acid (Normal=50-100%)				82.8
Collagen (Normal=50-100%)				82.9
Ristocetin-RIPA (Normal=50-100%)				75.9

Table 2: Classification of vonwillebrand disease

Type	Description
1	Partial quantitative VWF deficiency
2	Qualitative VWF deficiency
2A	Caused by mutations that decrease the proportion of large functional VWF multimers, leading to decreased VWF-dependent platelet adhesion
2B	Caused by mutations that pathologically increase platelet-VWF binding, leading to the depletion of large, functional VWF multimers; circulating platelets also are coated with mutant VWF, which may prevent the platelets from adhering at sites of injury
2M	Caused by mutations that decrease VWF-dependent platelet adhesion, but do not reduce the large VWF multimers; the distinction between 2A and 2M disease requires VWF multimer gel electrophoresis
2N	Caused by VWF mutations that impair binding to factor VIII, lowering factor VIII levels; often masquerades as an autosomal recessive form of hemophilia A; distinction from hemophilia A may require assays of factor VIII–VWF binding.
3	Virtually complete VWF deficiency and decreased factor VIII (1 to 9 IU per dL)

taken lightly in developing countries. Women are more affected due to this condition as they menstruate every month and end up with severe blood loss which may at times be life-threatening. Von Willebrand's disease should always be suspected in a case of menorrhagia to prevent life-threatening complications. Usually, type 1 VWD presents with mild mucocutaneous bleeds. Our patient presented with menorrhagia with severe anemia with no investigations evidence of bleeding or coagulation disorders, requiring blood transfusion which adds uniqueness to our case, and despite this being an autosomal dominant inherited condition there is no family history suggesting this condition in family members which suggests it could have been due to variable penetrance which is a rare phenomenon.

5. Source of Funding

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6. Conflict of Interest

None.

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Author biography

Rajani H S, Associate Professor https://orcid.org/0000-0001-5578-8729

Akshaya SV, Junior Resident

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